REMARKS

Status of Claims and Amendment

Claims 1 and 15-20 have been amended. Claims 1-9, 11 and 13-21 are all the claims pending in the application. Claims 10 and 12 are withdrawn as being directed to a non-elected invention.

Claims 1 and 15-20 have been amended to recite "resulting in clinical trial designs". Support for the amendments to claims 1 and 15-20 can be found, for instance, at 1st sentence of paragraph [0038], paragraph [0113], paragraph [0134] and Figures of the published application.

No new matter is added.

Response To Rejections Under 35 U.S.C. § 101

Claims 1-9, 11, and 13-21 are rejected under 35 U.S.C. § 101 as being allegedly directed to non-statutory subject matter.

The Office Action appears to assert that the claimed method is an "abstract idea" without a practical application that physically transforms an article or physical object to a different state, or provide a concrete, tangible, and useful result. The Office Action asserts that the claimed method merely provides steps of *in silico* information manipulation so that a physical transformation of matter is not shown.

The Office Action appears to assert that the determination of whether the claimed method provides a practical application is not focused on the steps taken, as it is focused on the final result achieved by the method. The Office Action states that a claim is statutory where it recites a result that is concrete (i.e., reproducible), tangible (i.e., communicated to a user), and useful (i.e., specific and substantial). In this regard, the Office Action asserts that the recited steps of

"performing clinical trials" do not provide a tangible result that is useful to one skilled in the art, and that these embodiments merely encompass *in silico* results with no specific output. The Office Action states that no real-world result is set forth, as the results could merely reside *in silico*, as the method steps are performed on a computer model.

Furthermore, the Office Action appears to assert that because the claimed method is not "limited to any particular apparatus of machinery", the claims do not satisfy the "machine or transformation test" set forth in *In re Bilski*.[1] The Office Action notes that according to *Bilski*, claim limitations that are directed to obtaining or outputting data using a generic apparatus or machine are considered insignificant pre-solution and post-solution activity, and would not meet the machine or transformation test.

In response, Applicants note that the claimed method allows for the transformation of raw data obtained either *in vitro*, *in vivo*, or from actual small clinical trials to provide an optimum treatment regimen or clinical trial design for cancer treatment that is representative of actual preclinical to Phase IV clinical trials without the expense and time loss usually associated with such full-scale studies.

Accordingly, contrary to the Office Action's assertions, the steps of the claimed method do not "merely encompass *in silico* results with no specific output" because the claimed method performs interactive clinical trials to test a new drug for cancer treatment. In this regard, the

[1] Bilski reaffirms the idea that the prohibition on patenting abstract ideas has two distinct aspects: (1) when an abstract concept has no claimed practical application, it is not patentable; (2) while an abstract concept may have a practical application, a claim reciting an algorithm or abstract idea can state statutory subject matter only if it is embodied in, operates on, transforms, or otherwise is tied to another class of statutory subject matter under 35 U.S.C. §101 (i.e. a machine, manufacture, or composition of matter). *(Gottschalk v. Benson,* 409 U.S. 63, 175 USPQ 673, 1972) *(In re Bilski,* Fed. Cir. 2008).

computer simulations are conducted in parallel with *in vitro* or *in vivo* studies, or actual small clinical trials on patients, and based upon the data obtained from these studies or small clinical trials, the *in silico* model may be adjusted by the user after each phase of the clinical trial in order to obtain a more precise and optimum treatment regimen or clinical trial design for the treatment of cancer. Specifically, prior to each step of the phase trials, computer simulation is performed to predict the results of the phase trials, and the predicted results are compared to *in vitro* or *in vivo* studies or actual clinical results corresponding to the step and the computer model is adjusted based on the comparison.

Accordingly, the algorithm used in the claimed method provides more accurate predictions because the algorithm is continuously validated and improved by information obtained in parallel from clinical trials. For instance, the claimed method performs a pre-clinical phase in which *in vitro* and *in vivo* data are inputted into the computer model and such data is transformed to provide data representative of the pharmacokinetics[2] and pharmacodynamics[3] of the drug (see specification at paragraph [0095] and Figure 5B). The *in silico* model is then adjusted based on a comparison of the results of the clinical trial and the computer simulation.

With regard to Phase I, based upon the cumulative effect of the drug, the user may adjust the *in silico* model to perform phase I clinical trials on at least a single dose in parallel with the computer simulation. For instance, during Phase I clinical trials, the *in silico* patient interacts

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[2] The effect of the body on the drug in terms of absorption and distribution of the administered drug, the rate at which the drug action begins and the duration of the effect, the chemical changes of the substance in the body (e.g. by enzymes) and the effects and routes of excretion of the metabolites of the drug.

[3] The biochemical and physiological effects of the drug on the body, the mechanisms of drug action, and the relationship between drug concentration and effect.

with the actual small clinical trial to determine a maximal tolerated dose, minimum effective dose, and a recommended dose (see Example 2 and Figures 5E to 55G) so that by the end of the Phase I trial, the transformed data results in a fully verified *in vivo* human model that contains all the data on the pharmacokinetics and pharmacodynamics obtained from the preclinical phase.

Since multiple simulations are performed using the computer model with different doses and dosing intervals, an optimal protocol or clinical trial design is determined for the most responsive patient populations and indications are provided for a Phase II clinical trial. Phase II clinical trial is performed where a number of small scale clinical trials are performed in parallel based on the preclinical and Phase I results. In addition, at the interim stage between phase I and phase II (Example 3), or phase II and phase III (Example 4), the computer model provides short-term predictions regarding the effects of drug administration schedules and allows the user to perform a search for mono- or combination therapy schedules that would yield the optimal response with the least toxicity for a cancer type. The interim results are analyzed to choose the most promising regimens for continued clinical trials. Further, the *in silico* model may be personalized based upon the patients involved in the actual clinical trials in order to yield more precise results. Based upon the information obtained in the Phase II clinical trial, Phase III clinical trials are performed for chosen indications by chosen protocols selected by the user (Example 4). The efficacy of the selected protocol is confirmed by the computer model in further Phase II trials (Example 4).

Thus, based on the specific result outputted at the end of each clinical trial step in the claimed method, the user may adjust the computer model in order to obtain the most effective treatment or clinical trial design. Also, even though the steps of "performing clinical trials" encompass *in silico* results, a tangible result is provided after each step in an "on-going dialogue"

with the user from the pre-clinical phase to phase IV clinical trials (see paragraphs [0047]-[0048]) in order to obtain an optimal treatment regimen or clinical trial design that is useful to one skilled in the art.

Accordingly, the claimed method (as recited in independent claims 15-20) produces improved clinical trial designs based on computer models and simulations calibrated on experimental data from previous clinical or preclinical trial phases. For instance, claim 19 produces Phase III clinical trial designs based upon a model adjusted by experimental data from the preceding clinical trial phases I and II. Claim 1 brings together the other mentioned claims to produce the entire clinical trial design for a cancer related drug, i.e., phase I is designed based on pre-clinical data and simulation results and once clinical trials at this Phase are performed the clinical results are used according to the present invention to design phase II, and so forth.

The claimed method is novel in combining virtual, or *in silico*, clinical trials with some experimental input in order to transform the current clinical trial designs to improved clinical trial designs, based on a combination of *in vitro* and/or *in vivo* and *in silico* methodology.

The performance of model based simulations in parallel to the experimental data enables evaluation of various clinical trial designs and selection of the ones most suitable in accordance with the specifications of the user. Further, the claimed method allows many alternative clinical designs to be tested and simulated. Only the clinical designs that qualify are selected to be experimentally performed in humans.

Thus, for at least the reasons discussed above, the presently claimed method provides a tangible result that is useful to one skill in the art

Nevertheless, and solely to advance prosecution of the present application, claims 1 and 15-20 have been amended to recite "resulting in clinical trial designs" to further clarify the result specific output obtained at the end of each clinical trial step of the claimed method.

Conclusion

In view of the above, reconsideration and allowance of this application are now believed to be in order, and such actions are hereby solicited. If any points remain in issue which the Examiner feels may be best resolved through a personal or telephone interview, the Examiner is kindly requested to contact the undersigned at the telephone number listed below.

The U.S. Patent and Trademark Office is hereby directed and authorized to charge all required fees, except for the Issue Fee and the Publication Fee, to Deposit Account No. 19-4880. Please also credit any overpayments to said Deposit Account.

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